SMALLPOX
Report Immediately

✓DISEASE AND EPIDEMIOLOGY

Clinical description:

Smallpox infection typically begins with a prodromal illness characterized by a high fever (102–104°F), malaise, headache, backache, and abdominal pain. This prodromal period typically lasts 2–4 days and leaves the patient often too sick to carry on with normal activities. A rash begins to develop after the prodromal period and the patient typically begins to feel better. The rash first appears as an enanthem, with tiny red spots developing inside the mouth that are often not noticeable. About 24 hours later the rash develops into an exanthem, beginning as macules on the face and spreading to the forearms, trunk, and legs within 24 hours. The rash follows a characteristic "centrifugal" pattern, with the highest concentration of lesions on the face and distal extremities, including the palms of the hands and soles of the feet. Over the next week the rash will slowly progress through successive stages of macules, papules, vesicles, pustules, and then crusted scabs. The center of the vesicles will tend to dimple, a presentation called "umbilication". Between the 7th and 10th day of the rash the pustules reach their maximum size. The pustules are deeply embedded in the skin, giving the feeling of small beads underneath the skin. 3-4 weeks after the rash onset the scabs begin to fall off leaving depigmented, often pitted scars.

- **Variola major** is the more severe form of the disease and can have four very different clinical presentations.
  - **Ordinary smallpox** occurs in more than 90% of unvaccinated cases and follows the clinical description described previously.
  - **Modified smallpox** occurs most often among previously vaccinated persons. The symptoms are generally less severe and the lesions are more superficial. This form of the disease is easily confused with chickenpox.
  - **Flat (malignant) smallpox** occurs in 5-10% of the cases and is characterized by lesions that remain flat when lesions during ordinary smallpox begin to form pustules. The fever remains elevated throughout the course of the disease, and the patient usually has severe toxemic symptoms. The lesions are soft and velvety to the touch and may contain hemorrhages.
  - **Hemorrhagic smallpox** is a severe, though uncommon, form of the disease that occurs more frequently in pregnant women and adults. Hemorrhagic manifestations can occur early or late in the disease and patients will bleed into the skin, GI tract, and mucus membranes.
- **Variola minor** is a much less severe form of the disease with a shorter duration.
- **Variola sine eruptione** or subclinical infection can occur among vaccinated contacts of a recent smallpox case. A fever, headache and sometimes a backache will develop and subside within 48 hours. Persons with subclinical infections have not been shown to transmit disease to others.

Causative agent:

Smallpox is caused by the variola virus, a DNA virus and a member of the Poxviridae family (genus *Orthopoxvirus*). The two clinical forms of the disease are caused by different strains of the virus.

Differential diagnosis:

The following table describes diseases and syndromes most commonly confused with smallpox.

Condition	Clinical Clues
Varicella (Chickenpox)	Most common in children < 10 years, children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash usually begins in dermatomal distribution
Impetigo (caused by *Streptococcus pyogenes* or *Staphylococcus aureus*)	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients usually not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye", or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands and feet
Erythema multiforme major (Stevens-Johnson syndrome)	Major form involves mucous membranes and conjunctivae; may be target lesions or vesicles
Enterovirus infection (particularly hand, foot, and mouth disease)	Summer and fall; fever and mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey, tender, flat, often oval vesicles; peripheral distribution
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites	Itching is a major symptom; patient is not febrile and is otherwise well
Molluscum contagiousum	May disseminate in immunosuppressed persons

CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize patients into high, moderate or low risk for smallpox. There are three major and five minor smallpox criteria:

Major criteria

1. The patient has had a febrile prodrome (temperature 101°F [38.3°C]) or higher) 1–4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain.
2. Rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent as they evolve.
3. On any one part of the body all the lesions are in the same stage of development (i.e., all are vesicles or all are pustules).

Minor criteria

1. The distribution of the rash is centrifugal (i.e., the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk).
2. The first lesions of the rash appear on the oral mucosa or palate, or on the face or forearms.
3. The patient appears toxic or moribund.
4. Lesions have progressed slowly (i.e., the individual lesions evolved from macules to papules to pustules, each stage lasting 1–2 days).
5. Lesions are present on the palms or soles.

A person is considered at **high risk** for smallpox if he or she meets all three major criteria. Immediate action should be taken to make sure that contact precautions and respiratory isolation are implemented. These patients should be reported to local and/or state health authorities immediately. Obtain digital photographs if possible, and consult with dermatology and/or infectious disease experts. Following such consultation, if the patient is still considered to be at high risk, the state health department will immediately report the case to CDC and arrangements will be made for laboratory testing for smallpox virus.

A person considered at **moderate risk** for smallpox must have a febrile prodrome and either one other major criterion or four or more minor criteria. These patients should be isolated and be evaluated urgently to determine the cause of the illness. Persons classified as high or moderate risk should be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible.

Any person who did not have a febrile prodrome is considered at **low risk**, as are persons who had a febrile prodrome and fewer than four minor criteria. These patients should be managed as clinically indicated.

Laboratory identification:

Variola virus can be detected in vesicular or pustular fluid by culture or PCR. The diagnosis of an *Orthopoxvirus* infection can be made rapidly by electron microscopic examination of dried vesicular fluid on a microscope slide, but does not distinguish between vaccinia, variola and other poxvirus infections. PCR and culture testing will confirm the diagnosis.

Laboratory testing for smallpox is warranted only once a case is classified as high risk. For cases that meet the moderate risk classification, the most important laboratory procedure is varicella-zoster virus testing.

NOTE: UPHL is capable of testing all specimens to rule-out smallpox. Testing for smallpox must be coordinated with UDOH, who will work with UPHL and CDC to determine the best course of action.

Treatment:

There is no specific treatment for smallpox. Cidofovir has been suggested as having a role in smallpox therapy, but data to support this claim is unavailable.

Case fatality:

- **Variola major** has a case fatality rate of 20–50% or more in unvaccinated populations.
- **Hemorrhagic** and **flat (malignant) smallpox** are usually fatal.
- **Variola minor** has an overall case-fatality rate of less than 1%.

Reservoir:

Humans are the only known reservoir for the variola virus.

Transmission:
Transmission occurs primarily from through the spread of respiratory droplets. However, transmission may occur through direct contact with an infected person or contact with an object soiled with infectious particles

Susceptibility:
Routine vaccination in the US for smallpox stopped in 1972. Those who have previously been vaccinated are most likely still immune; however susceptibility among the unvaccinated is universal. Selected military, research, and medical personnel are immune to the disease because of vaccination.

Incubation period:
The incubation period from exposure to prodrome averages 12 days, with a range of 7-17 days, with 2-4 additional days for rash onset.

Period of communicability:
An infected person is generally contagious for three weeks, from the development of the earliest lesions in the mouth to the disappearance of all scabs. The first week of rash illness is the most infectious period.

Epidemiology:
The last case of naturally-acquired smallpox in Utah, the US, and the world occurred in 1945, 1949, and 1977 (in Somalia), respectively. The last two cases of smallpox in the world occurred in 1978 in England and were associated with a breach in laboratory safety. In 1980, global eradication of smallpox was certified by the World Health Organization. Currently, two WHO reference laboratories (the CDC and the Institute of Virus Preparations in Moscow, Russia) hold variola virus stocks under strict security. All laboratory work with the smallpox virus is done under strict biosafety level 4 procedures.

✓PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:
- Conduct rash surveillance.
- Identify all cases and susceptible exposed people rapidly.
- Assure that appropriate testing protocols are followed.

Prevention:
Environmental Measures
If a patient presents to an emergency department, clinic, or doctor's office with an acute generalized vesicular or pustular rash illness, care should be taken to decrease the risk of disease transmission. Patients should not be left in common waiting areas. The patient should be assessed to determine whether there is a high, medium, or low risk of smallpox.

1. If in a doctor's office or clinic, the patient should be placed immediately in a private room with the door kept shut.
2. When admitted or while being held for observation, the facility should institute appropriate airborne isolation and contact precautions and should alert the infection

control department. The patient should be placed in a private room at negative pressure to the rest of the facility (airborne infection isolation). The door should be kept closed at all times, except when staff or the patient must enter or exit.

3. Staff and visitors, regardless of vaccination status, should wear properly fitted respirators (N95 or higher level of protection), gloves, and gowns.
4. The patient should wear a surgical mask whenever he/she must be outside of the negative pressure isolation room and must be gowned or wrapped in a sheet so that the rash is fully covered.

Chemoprophylaxis:

Vaccination after exposure to smallpox has reduced the rate of secondary cases in households by up to 91% when compared to unvaccinated household members. Secondary attack rates were lowest among contacts that were vaccinated within 7 days of their exposure. Contacts that did develop disease usually had much milder symptoms (modified smallpox).

Vaccination:

The smallpox vaccine is made from a related orthopox virus – the vaccinia virus. The vaccine is highly effective at inducing immunity against smallpox when administered effectively prior to exposure. Smallpox vaccine production ceased in the early 1980s, and current supplies of smallpox vaccine are limited. However, recent studies have demonstrated that vaccines stored in the 1960s and 1970s still have excellent potency, even when diluted. New cell-culture-grown smallpox vaccines will become available soon.

Because the smallpox vaccine is a live-virus vaccine, vaccinia virus is present at the site of vaccination beginning about 4 days after vaccination. Viral shedding from the vaccination site usually occurs 4–14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin. Therefore, appropriate hand hygiene and/or keeping the vaccination site covered with a bandage is necessary to prevent transmission of the virus to contacts of the vaccinee.

Isolation and quarantine requirements:

Isolation: Cases should be placed on standard, contact, and airborne isolation until lesions have dried and crusts have separated.

Hospital: Cases should be placed on standard, contact, and airborne isolation. The patient should be placed in a private, airborne infection isolation room with negative pressure ventilation with high-efficiency particulate air filtration. Cases should remain isolated until lesions have dried and crusts have separated.

Quarantine: Afebrile contacts shall be placed under fever surveillance (quarantine) for 18 days from the last contact or 14 days from successful vaccination (whichever comes first), with monitoring and recording of temperature occurring twice daily (morning and evening). Febrile contacts with or without rash shall be considered the same as a case and shall be handled in the same fashion (isolation). If no rash develops after five days and the fever is diagnosed as being caused by recent vaccination or some other non-smallpox etiology, the contact may be released from isolation to home but with continued fever surveillance for 18 days following their last contact with a case or 14 days following successful vaccination (whichever comes first).

✓CASE INVESTIGATION

Reporting:

If smallpox were to reoccur in the U.S. or elsewhere, the most likely circumstances of reintroduction are generally accepted to be:

- An unintentional infection in a laboratory. Currently there are only two WHO-approved smallpox virus research and repository laboratories: the CDC in Atlanta, Georgia and the Institute of Virus Preparations in Moscow, Russia. There is speculation, however, that stockpiles of variola virus may exist elsewhere.
- A bioterrorist attack involving deliberate infection of a person.
- A bioterrorist attack involving intentional release of smallpox virus into the environment.

If smallpox is at all suspected, it should be reported immediately to the local health department or the Utah Department of Health. Adverse events following smallpox vaccination are also reportable.

Case Definition:

Smallpox (pre-event definition):

(This definition is to be used for pre-event surveillance. It is more sensitive and less specific than the definition developed by CSTE, which is to be used only for post-event surveillance)!

Clinical Case Definition

An illness with acute onset of fever ≥101°F (38.3°C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause.

Laboratory criteria

- Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, or
- Isolation of smallpox (variola) virus from a clinical specimen *with* variola PCR confirmation.

Note: Laboratory diagnostic testing for variola virus should be conducted in a CDC Laboratory Response Network (LRN) laboratory utilizing LRN-approved PCR tests and protocols for variola virus. Initial confirmation of a smallpox outbreak requires additional testing at CDC.

Note: The importance of case confirmation using laboratory diagnostic tests differs depending on the epidemiological situation. Because of the low predictive value of a positive lab test result in the absence of a known smallpox outbreak, in the pre-outbreak (pre-event) setting, laboratory testing should be reserved for cases that meet the clinical case definition and are thus classified as being a potential high risk for smallpox according to the rash algorithm poster (www.bt.cdc.gov/agent/smallpox/diagnosis/evalposter.asp).

Case Classification

Suspect: A case with a febrile rash illness with fever preceding development of rash by 1-4 days.

Probable: A case that meets the clinical case definition, or a case that does not meet the clinical case definition but is clinically consistent with smallpox and has an epidemiological link to a confirmed case of smallpox. Examples of clinical

presentations of smallpox that would not meet the ordinary type (pre-event) clinical case definition are: a) hemorrhagic type, b) flat type, and c) variola sine eruptione.

Confirmed: A case of smallpox that is laboratory confirmed, or a case that meets the clinical case definition that is epidemiologically linked to a laboratory confirmed case.

Smallpox (2004 – post-event definition):

(This definition is to be used only during post-event surveillance)!

Clinical case definition:

An illness with acute onset of fever ≥101º F (≥38.3 º C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause. Clinically consistent cases are those presentations of smallpox that do not meet this classical clinical case definition: a) hemorrhagic type, b) flat type, and c) *variola sine eruptione*.

Laboratory criteria for diagnosis:

- Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, or
- Isolation of smallpox (variola) virus from a clinical specimen (Level D laboratory only; confirmed by variola PCR).

Note: Indications for laboratory testing of patients with suspected smallpox should be followed as described in detail in Guide A of the CDC Smallpox Response Plan. Laboratory diagnostic testing for variola virus should be conducted in Level C or D laboratories only.

Case Classification

Suspect: A case with a generalized, acute vesicular or pustular rash illness with fever

preceding development of rash by 1-4 days.

Probable: A case that meets the clinical case definition, or a clinically consistent case that does not meet the clinical case definition and has an epidemiological link to a confirmed case of smallpox.

Confirmed: A case of smallpox that is laboratory confirmed, or a case that meets the clinical case definition that is epidemiologically linked to a laboratory confirmed case.

Exclusion Criteria:

A case may be excluded as a suspect or probable smallpox case if an alternative diagnosis fully explains the illness or appropriate clinical specimens are negative for laboratory criteria for smallpox.

Case investigation process:

- Fill out a morbidity form
- Assure that all case contacts are identified and appropriately managed

Outbreaks:

Since smallpox no longer exists as a naturally occurring disease, a single laboratory confirmed case of smallpox would be considered an outbreak and an extensive response involving many different federal, state, and local agencies would be warranted.

Identify case contacts:

For the purposes of smallpox surveillance and case investigation, a "contact" is defined as follows:

Contact: A person who has been exposed to the risk of infection.
Primary contact: A person with contact with a confirmed, probable, or suspect case of smallpox during the infectious period. Primary contacts include both household and non-household contacts. Risk of smallpox transmission is increased with increased duration of face-to-face contact of less than two meters (≤6.5 feet).
Household contact: A person who lives or works in the same household as the case.
Non-household contact: A person who does not live or work in the case's household.
Secondary contact: A household member of a primary contact, a non-household contact, and a person who works in the household of a primary contact.

Priority categories for contacts, from highest priority to lowest, are as follows:

1. Case's household family members and others spending three or more hours in the household since the case's onset of fever.
2. Non-household members with contact 2 meters or less (≤6.5 feet) with case with rash for 3 or more hours.
3. Non-household members with contact 2 meters or less (≤6.5 feet) with case with rash for fewer than 3 hours.
4. Non-household members with any contact with case with rash for three or more hours.
5. Non-household members with any contact with case with rash for fewer than three hours.

(The above information is taken from the CDC's *Smallpox Response Plan and Guidelines*.)

Case contact management:

Vaccinating and monitoring contacts of cases and family contacts of contacts will help to protect those at greatest risk for contracting the disease as well as form a buffer of immune individuals to prevent the spread of disease. Large-scale vaccination in potentially exposed communities may become necessary, although it is crucial that cases be identified and isolated. Large-scale vaccination might also be applied to unaffected communities to protect against further spread of smallpox and additional releases as well as to build the public's confidence in its protection and ability to return to normal activities.

Contact Tracing

Contact tracing should include the following steps:

1. Trace each contact whose name, address, and/or telephone number is known.
2. Use work and school contact numbers, telephone directories, voting lists, neighborhood interviews, site visits, "hangouts," etc., to trace contacts when contact information is unknown or incomplete. If contacts cannot be found through these mechanisms, other sources for notification of potential contacts (such as media announcements) may have to be considered.
3. Locate and interview each primary contact to confirm contact with the suspect, probable, or confirmed smallpox case, the presence or absence of symptoms in the contact (fever and/or rash), and to identify additional contacts that may not have been listed by the case.

4. Identify household contacts of each primary contact of the smallpox case (secondary contacts).
5. Arrange for immediate vaccination of each primary contact and their household contacts (secondary contacts). Either vaccinate contacts in the household (if this is feasible with the vaccine supply, security issues, and resources), or provide a vaccination ticket with identifying information and designate a vaccination facility for the contact(s) to attend as soon as possible. It is extremely important for smallpox outbreak control to prioritize the vaccination of contacts. In the past, when vaccination was done in the household, the task was given priority over transportation of a case to an isolation facility.
6. If the primary contact is symptomatic with fever or rash, arrangements should be made for prompt vaccination and transportation of the contact to a Type C facility (capable of isolating contagious individuals) or other designated evaluation site for medical evaluation to rule out smallpox. Contacts with symptoms should be counseled, interviewed, and reported as suspect cases using the appropriate smallpox surveillance (case reporting) form, and their contacts should be identified, interviewed, and vaccinated as soon as possible.
7. If the primary contact does not have a fever or rash, vaccinate or arrange for prompt vaccination, and place the contact under surveillance (quarantine) so that if the contact develops a fever or rash, he/she is immediately isolated and evaluated and does not expose other persons to smallpox (see #8 below).
8. If a household member cannot be vaccinated because of contraindications, the household member should be instructed to avoid physical contact with the primary contact until the incubation period of the disease has passed (18 days) or all vaccinated persons in the household are non-infectious for vaccinia virus (after the scab at the vaccine site has separated, 14–21 days after vaccination).
9. Each household contact should be provided with a vaccination ticket and instructed to attend a designated vaccination clinic site as soon as possible.
10. If any contacts have left the state, the contact tracers should notify the supervisor responsible for out-of-state contacts. The supervisor will then notify the appropriate authorities.

Numerous forms and work sheets have been created to facilitate the activities above. These are available on the CDC website at www.bt.cdc.gov/agent/smallpox/exposure .

Surveillance (Monitoring) of Health Status and Vaccine "Take" of Contacts

Surveillance of contacts of a case of smallpox will be conducted for early signs of smallpox disease (fever on two consecutive days and/or rash) and for vaccine "take." Contacts will be provided with a health department phone number to call if they develop any of the severe vaccine adverse reactions shown on the **Vaccine Information Statement**. Ideally, and if resources are available, primary contacts who do not have fever or rash at the time of interview should remain under active surveillance for 21 days after their last contact with the smallpox case or 14 days following successful vaccination.

(The above information is taken from the CDC's *Smallpox Response Plan and Guidelines*.)

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